

# The Relationship between Anti-Cyclic Citrullinated Peptide Positivity and Clinical/Radiological Findings in Patients with Psoriatic Arthritis

Psoriatik Artritli Hastalarda Anti-Siklik Sitrülinli Peptit Pozitifliği İle Klinik/Radyolojik Bulgular Arasındaki İlişki

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Geliş Tarihi / Received : 19.10.2021

Kabul Tarihi / Accepted: 02.07.2022

Çevrimiçi / Online: 28.12.2022

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Cite this article/Atf: Işık ÖÖ, Coşan F, Yazıcı A, Çefle A. The Relationship between Anti-Cyclic Citrullinated Peptide Positivity and Clinical/Radiological Findings in Patients with Psoriatic Arthritis, Sakarya Tıp Dergisi 2022 ;12(4): 687-693 DOI: 10.31832/smj.996517

## Öz

Psoriatic arthritis (PsA) is a chronic inflammatory disease in the spondyloarthropathy group. Although some PsA findings are similar to rheumatoid arthritis (RA), rheumatoid factor negativity, some radiological and clinical findings are different in PsA. There is no specific laboratory examination for diagnosis of PsA. On the other hand, anti-cyclic citrullinated peptide (anti-CCP) antibody positivity is a specific finding for the diagnosis of RA.

**Objectives** We aimed in this study to analyse the frequency of anti-CCP positivity in PsA and the association with clinical and radiological findings.

**Methods** The study group is consisted of 100 PsA patients, who fulfilled the CASPAR criteria for PsA and 100 healthy controls (HC). We filled a form for all patients, which included clinical and laboratory findings of patients. We analyzed anti-CCP antibody with micro-ELISA in the sera of patients.

**Results** In our study, the anti-CCP positivity was detected in 15% of PsA group and 4% of healthy controls. The difference was statistically significant ( $p=0,014$ ;  $OR=4,24$ , 95%  $CI=1,35-13,25$ ). Nine out of 15 anti-CCP positive patients were female, the remaining 6 were male. Thirteen patients (86,7%) had peripheral arthritis, 1 patient (6,7%) had sacroiliitis, 1 patient (6,7%) had peripheral arthritis and sacroiliitis. 42,8% of PsA patients with peripheral arthritis had asymmetric oligoarthritis (6/14), 28,5% had monoarthritis (4/14) and 28,5% had symmetric polyarthritis (4/14). Anti-CCP antibody positivity had no effect on the involvement of peripheral arthritis. Sacroiliitis and dactylitis were more frequent in the anti-CCP negative group. No patient with dactylitis had anti-CCP positivity ( $p=0,005$ ). While, 43,5% of RF positive patients were detected anti-CCP positivity, 6,5% of RF negative patients were detected anti-CCP positivity ( $p=0,000$ ).

**Conclusions** Our data reveals that anti-CCP positivity is more frequent in PsA compared to HC. However, we found no statistical association between anti-CCP positivity and clinical or radiological findings.

**Key words** Psoriatic Arthritis; Anti-Cyclic Citrullinated Peptide; Rheumatoid Factor

## Abstract

Psoriatik artrit (PsA), spondilartropati grubundaki kronik inflamatuvar bir hastalıktır. Bazı PsA bulguları romatoid artrit (RA) ile benzer olmasına rağmen, romatoid faktör negatifliği ile bazı radyolojik ve klinik bulgular PsA'da farklıdır. PsA tanısı için özel bir laboratuvar testi yoktur. Öte yandan anti-siklik sitrülüne peptit (anti-CCP) antikor pozitifliği RA tanısı için spesifiktir.

**Amaç** Bu çalışmada PsA'da anti-CCP pozitifliğinin sıklığını, klinik ve radyolojik bulgularla ilişkisini incelemeyi amaçladık.

**Yöntemler** Çalışma grubu, PsA için CASPAR kriterlerini karşılayan 100 PsA hastası ve 100 sağlıklı kontrolden (SK) oluşmaktadır. Tüm hastalar için, klinik ve laboratuvar bulgularını içeren bir form doldurduk ve hastaların serumlarında anti-CCP antikorunu mikro-ELISA yöntemi ile analiz ettik.

**Bulgular** Çalışmamızda PsA grubunun %15'inde ve sağlıklı kontrollerin %4'ünde anti-CCP pozitifliği saptandı. Fark istatistiksel olarak anlamlıydı ( $p=0,014$ ;  $OR=4,24$ , %95  $GA=1,35-13,25$ ). 15 anti-CCP pozitif hastanın dokuzu kadın, geri kalan 6'sı erkekti. On üç hastada (%86,7) periferik artrit, 1 hastada (%6,7) sakroiliit, 1 hastada (%6,7) periferik artrit ve sakroiliit vardı. Periferik artritli PsA hastalarının %42,8'inde asimetrik oligoartrit (6/14), %28,5'inde monoartrit (4/14) ve %28,5'inde simetrik poliartrit (4/14) vardı. Anti-CCP antikor pozitifliğinin periferik artrit tutulumu üzerine etkisi yoktu. Anti-CCP negatif grupta sakroiliit ve daktilit daha sıkı. Daktilitli hiçbir hastada anti-CCP pozitifliği yoktu ( $p=0,005$ ). RF pozitif hastaların %43,5'inde anti-CCP pozitifliği saptanırken, RF negatif hastaların %6,5'inde anti-CCP pozitifliği saptandı ( $p=0,000$ ).

**Sonuç** Verilerimiz, SK'lere kıyasla PsA'lı hastalarda anti-CCP pozitifliğinin daha sık olduğunu ortaya koymaktadır. Ancak, anti-CCP pozitifliği ile klinik veya radyolojik bulgular arasında istatistiksel bir ilişki bulunmamıştır.

**Anahtar Kelimeler** Psoriatik Artrit, Anti-Siklik Sitrülinli Peptit, Romatoid Faktör



## INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease in the spondyloarthropathy group, accompanied by psoriasis in the history of the patient or family.<sup>1</sup> PsA can be distinguished from rheumatoid arthritis (RA) by the presence of specific radiographic findings, negative rheumatoid factor (RF), and clinical differences. Unlike rheumatoid arthritis (RA), there is no significant loss of periarticular bone mineralization in PsA. PsA shows significant bone resorption as well as new bone formation in the joint due to a disrupted bone turnover in the same finger.<sup>2</sup> Although there are some reports determined a slight increase in RF levels in PsA patients, it is generally negative.<sup>3</sup> There is no laboratory test specific to PsA. The positivity of RF and anti-cyclic citrullinated peptide (anti-CCP) antibody is important in the diagnosis of RA. Anti-CCP antibodies were initially described as anti-perinuclear factors and later as anti-keratin and anti-filaggrin antibodies.<sup>4,5</sup> These antibodies were detected by enzyme-linked immunosorbent assay (ELISA) using cyclic citrulline peptide. The sensitivity of the test is also increased with second generation ELISA tests. The specificity and sensitivity of the anti-CCP test for RA has been investigated in several studies.<sup>6</sup> These antibodies have rarely been detected in other rheumatic diseases such as Sjogren syndrome<sup>7</sup>, systemic lupus erythematosus (SLE)<sup>8</sup> and juvenile idiopathic arthritis.<sup>9,10</sup> Many years before the onset of RA and very early in the disease process, anti-CCP antibodies were found to be positive.<sup>11-13</sup> In addition, the disease is more erosive in patients with anti-CCP positive RA.<sup>6</sup> In other rheumatologic diseases, the specificity of anti-CCP antibodies is quite low compared to RA.<sup>6,14-16</sup> However, the prognostic value of anti-CCP antibodies for PsA is not clearly known. First, in a study conducted in 2005, anti-CCP antibody positivity was found in 7.8% of patients with PsA.<sup>17</sup> In subsequent studies, there were conflict results about the relationship between serology positivity and clinical/radiological findings.<sup>18-23</sup> In this study, we aimed to assess anti-CCP in patients with PsA and healthy adult control group and to evaluate the relationship between anti-CCP positivity and clinical and

radiological findings.

## MATERIALS and METHODS

The study included 100 PsA patients who were admitted to our rheumatology outpatient clinic, and who had examined anti-CCP and RF. As control group, 100 healthy subjects without any known chronic and infectious diseases were included in this study. All patients fulfilled the criteria defined by the CASPAR study group.<sup>24</sup> Study protocol was approved by Kocaeli University Local Ethics Committee. The study was performed according to the Declaration of Helsinki.

The demographics, clinical characteristics, treatment and outcomes of patients were abstracted from medical records. General physical examinations and joint examinations of the patients were performed at admission to the outpatient clinics and their responses to the current treatments were evaluated using psoriatic arthritis response criteria (PSARC).<sup>25</sup> The cut-off of anti-CCP is 5 IU/ml and 20 RU/ml for anti-CCP positivity and RF, respectively.

### Statistical Analysis

The data collected were evaluated with SPSS 13.0 for Windows program. Data were analyzed using chi-square test/Fisher's exact test for categorical variables and Mann-Whitney-U test for continuous variables.

## RESULTS

100 patients with diagnosis of PsA (61 females, 39 males) and 100 healthy adults (62 females, 38 males) without any known diseases were included in the study. Gender distribution of the groups was similar ( $p=1.0$ ). The mean age was  $44.11\pm 13.45$  (min-max: 20-73) years in patients with PsA, and was  $40.55\pm 11.57$  (min-max= 21-70) years in healthy adults.

In patients with PsA, the mean age of onset was  $31.79\pm 13.3$  (min-max= 5-67) years for psoriasis and was  $37.96\pm 12.72$  (min-max=15-69) years for PsA. The mean duration

of disease in patients with PsA was  $73.2 \pm 55.9$  (min-max=7-312) months, and the mean interval time between the onset of complaints and treatment was  $24.49 \pm 36.23$  (min-max=1-190) months. The mean interval time between psoriasis and PsA was  $87.95 \pm 116$  (min-max=0-840) months. The mean follow-up period was  $36.4 \pm 32$  (min-max=2-140) months.

There was no family history of psoriasis in 73% of the patients with PsA. 23% of the patients had first-degree relatives with psoriasis, while 4% had second-degree relatives with psoriasis. Of the patients, 3% had a family history of ankylosing spondylitis.

Peripheral joint involvement was observed in 80% of the patients with PsA, isolated spondylitis in 7% and both in 13%. Anti-CCP was positive in 15% of PSA patients. Nine out of 15 anti-CCP positive patients were female, the remaining 6 were male. Thirteen patients (86,7%) had peripheral arthritis, 1 patient (6,7%) had sacroiliitis, 1 patient (6,7%) had peripheral arthritis and sacroiliitis. 42,8% of PsA patients with peripheral arthritis had asymmetric oligoarthritis (6/14), 28,5% had monoarthritis (4/14) and 28,5% had symmetric polyarthritis (4/14) (Table-1).

While anti-CCP was positive in 15% of the patients with PsA, it was positive in 4% of healthy controls, and this difference was statistically significant ( $p=0.014$ ; OR=4.24, 95% CI=1.35-13.25). There was no significant difference between two groups in terms of RF positivity. RF was positive in 20% of the patients in the control group, and positive in 23% of the patients with PsA ( $p=0.606$ ; OR=1.19, 95% CI=0.61-2.35) (Table 2).

Anti-CCP was positive in 9.8% of females with PsA and 23.1% of males. Although the difference was not statistically significant, anti-CCP positivity was found to be more frequent in male patients ( $p=0.071$ ).

Anti-CCP was determined to be positive in 17.5% of the

patients with chronic arthritis and 13.3% of the patients without chronic arthritis. The relation between anti-CCP positivity and the development of chronic arthritis was not statistically significant ( $p=0.568$ ), however it was observed that anti-CCP positivity increased the development of chronic arthritis.

Table 1: Clinical features of patients		
n (%)	All PsA Patients N=100	PsA patients with anti-CCP positivity N=15
Type of joint involvement		
Peripheral arthritis	80 (80)	13(86.7)
Spondylitis	7 (7)	1(6.7)
Peripheral arthritis + spondylitis	13 (13)	1(6.7)
Peripheral Arthritis (n: 80)		
Monoarthritis	10 (10.7)	4/14(28.5)
Asymmetric oligoarthritis	50 (53.7)	6/14(42.8)
Asymmetric polyarthritis	4 (4.3)	-
Symmetrical polyarthritis	29 (31.1)	4/14(28.5)
Chronic Arthritis	40 (40)	7(46.7)
Enthesitis	26 (26)	3(20)
Dactylitis	30 (30)	0
Nail involvement	21 (21)	3(20)
Uveitis	3 (3)	1(6.7)
Deformity	22 (22)	4(26.7)
PSARC response	85 (85)	13(86.7)
Radiological changes in peripheral arthritis (n: 80)		
Arthritis mutilans	1 (1.5)	0
Erosion	7 (10.9)	
Ankylosing	7 (10.9)	
Biological agents using	31 (31)	4(26.7)
Reason for biological agent (n:31)		
Spondylitis	11 (35.5)	1(6.7)
Resistant peripheral arthritis	16 (52.75)	3(20)
Resistant psoriasis	4 (12.9)	
csDMARD treatment		
Methotrexate	93 (93)	14(93)
Leflunomide	11 (11)	4(26.7)
Sulfasalazine	5 (5)	1(6.7)
PSARC: Psoriatic Arthritis Response Criteria, csDMARD: conventional synthetic Disease Modifying Anti-Rheumatic Drugs		

**Table 2:** Comparison of groups in terms of Anti-CCP and RF Positivity

n (%)	PsA (n=100)	Healthy Control (n=100)	p	OR	%95 CI
Anti-CCP positivity	15 (15)	4 (4)	0.014	4.24	1.35-13.25
RF positivity	23 (23)	20 (20)	0.606	1.19	0.61-2.35

Anti-CCP: anti-cyclic citrullinated peptide, RF: rheumatoid factor, PsA: psoriatic arthritis

Anti-CCP positivity was found in 10% of the patients with sacroiliitis (p=0.729). The frequency of sacroiliitis was found to be higher in patients with anti-CCP negative. Anti-CCP was found to be positive in 29.4% of the patients who had no psoriasis or had PsA before appearance of psoriatic lesions (p=0.068). Anti-CCP positivity was not detected in any of the patients with dactylitis (p=0.005).

Anti-CCP positivity was found in 43.5% of the patients with positive RF and only in 6.5% of the patients with negative RF (p = 0.000). It was observed that RF positivity increased the probability of anti-CCP positivity by 11-fold. In the logistic regression analysis, a significant relationship

was found between anti-CCP positivity and only RF positivity. (Table-3)

No effect of anti-CCP positivity on peripheral arthritis involvement was determined (p=1.0). No correlation was found between anti-CCP positivity and whether remission in joint involvement was observed during follow-up (p=0.168). There was no significant relationship between elevated anti-CCP levels and elevated erythrocyte sedimentation rate (ESR) (p = 0.304), elevated C reactive protein (CRP) (p = 0.771), and use of biological agents (p = 0.772). There was no correlation between PSARC response evaluation and anti-CCP positivity (p = 1.0). There was no correlation between anti-CCP positivity and the presence of typical radiological findings in patients with peripheral arthritis (p = 0.207).

Anti-CCP mean of 15 patients were 9.86 +33.3 (min-max= 5.2-200). Anti CCP was found 2 times the upper limit in 13% of the patients and 3 times and above in 40%. However, no significant relationship was found, especially when the high anti-CCP titer was compared with clinical and laboratory data.

**Table 3:** According to Logistic regression model effect of anti-CCP Positivity on Findings

n (%)		CCP (-) (n=85)	CCP (+) (n=15)	p	OR	%95 CI
Gender	Women	55 (64.7)	6(40)	0.071	2.75	0.89-8.47
	Male	30 (35.3)	9(60)			
Chronic arthritis		33(38.8)	7(46.7)	0.568	1.39	0.46-0.42
Deformity		18(21.2)	4(26.7)	0.736	1.35	0.385-4.76
Sacroiliitis		18(21.2)	2(13.3)	0.729	1.75	0.36-8.15
Nail Involvement		18(21,2)	3(20)	0.918	1.075	0.27-4.22
Psoriasis		79(93)	12(80)	0.123	0.42	0.14-1.26
Low- response to treatment		4(4.7)	1(6.7)	0.168	2.44	0.72-8.29
Need for biological agents		27(31.8)	4(26.7)	0.077	0.78	0.23-2.67
High ESR		28(32.9)	7(46.7)	0.178	1,78	0.59-5.40
High CRP		29(34.1)	6(40)	0.771	1.29	0.42-3.97
RF positivity		13(15.3)	10(66.7)	0.000	11.08	3.25-37.70
PSARC response		72(84.7)	13(86.7)	1	0.85	0.17-4.23
Typical radiological changes in peripheral arthritis		13(15.3)	0	0.207	0.83	0.75-0.91

ESR: erythrocyte sedimentation rate, CRP: C reactive protein, RF: rheumatoid factor, PSARC: Psoriatic Arthritis Response Criteria

## DISCUSSION

PsA is a chronic inflammatory disease in the spondyloarthropathy group, accompanied by psoriasis in the history of the patient or family.<sup>1</sup> There is no PsA-specific laboratory test for the assessment of inflammatory activity in patients with PsA. In this study, healthy control group and the patients with PsA were compared in terms of anti-CCP positivity, and its clinical and radiological significance was emphasized.

Alenius et al. reported that the prevalence of anti-CCP was increased in psoriasis patients with arthritis compared with those without arthritis, but the prevalence was significantly lower than the patients with early RA. They found anti-CCP positivity in only eleven (6.8%) of 160 patients with PsA, and found that most of these patients met the ACR criteria for RA in 4-year follow-up period. Although anti-CCP positive PsA patients with morning stiffness, RF positivity and small joint involvement meet the RA criteria, they also have typical clinical features of PsA, and it was thought that RA and PsA may coexist in the same patient.<sup>18</sup> In a study by Vander Cruyssen et al., anti-CCP antibodies were found to be positive in 7.8% of the patients with PsA.<sup>17</sup> In a similar study, Abdel Fattah et al. reported that anti-CCP was positive in 17.5% of the patients with PsA, and high serum concentrations of anti-CCP in these patients were significant when compared with psoriasis patients without arthritis and healthy controls.<sup>23</sup> Similarly, in our study, anti-CCP positivity was found to be significantly higher in patients with PsA than in control group ( $p=0.014$ ). In our study, 15% rate of anti-CCP positivity was determined in patients with PsA, although this was higher than the rate reported by Alenius et al. and Vander Cruyssen et al., it was similar to the rate reported by Abdel Fattah et al.

In the study of Vander Cruyssen et al., although they had similar disease duration and similar treatments, anti-CCP positive patients had more joint involvement than anti-CCP negative patients. RF positivity was found in some

of these patients.<sup>17</sup> It is thought that RA may be detected simultaneously in patients with typical PsA who had co-existing anti-CCP and RF positivity, and probably that RA may have a higher prevalence in patients with PsA than in the general population.<sup>26</sup> Abdel Fattah et al. reported in their study that symmetrical polyarthritis, limitation of movement and deformity in small peripheral joints were significantly higher in patients with anti-CCP positive PsA than anti-CCP negative patients.<sup>23</sup>

In our study, no effect of anti-CCP positivity on peripheral arthritis involvement was detected. Peripheral arthritis was present in 14 of 15 patients with PsA, but four of them had symmetrical polyarthritis. This involvement was found to be similar to RA like in the group with symmetrical polyarticular involvement, which was also mentioned in Moll and Wright's classification.<sup>27</sup> In our study, anti-CCP was found to be positive in 17.5% of the patients with chronic arthritis and 13.3% of the patients without chronic arthritis. Although the difference between anti-CCP positivity and the development of chronic arthritis was not statistically significant, and anti-CCP positivity was found to increase the development of chronic arthritis. In studies conducted, axial involvement was found in 5-36% of the patients with PsA.<sup>28-31</sup> In our study, axial involvement was found in 20% of the patients and anti-CCP was found to be positive in 10% of these patients ( $p=0.729$ ). The frequency of sacroiliitis was defined higher in anti-CCP negative patients. Dactylitis is one of the important features of patients with PsA, and it has been reported with a rate of 5.6-53% in the studies.<sup>24,31,32</sup> Dactylitis, which is commonly seen in PsA and reactive arthritis, was present in 30% of the patients in our study; however, none of the anti-CCP positive patients had dactylitis ( $p=0.005$ ). The increased frequency of sacroiliitis in anti-CCP negative patients and the absence of dactylitis in anti-CCP positive patients suggests that the seropositive group had less features of the spondyloarthropathy group.

Korendowych et al. found an association between an-

ti-CCP positivity and radiological findings in patients with PsA, and found that all anti-CCP positive patients had erosions in their hands and feet. In the same study, a similar association was also demonstrated in patients with RA, and the authors found that anti-CCP positivity showed an erosive course in the future. In the same study, patients with anti-CCP positive PsA were found to have more swollen joints, and DMARD requirements of these patients were higher than those with anti-CCP negative PsA. It was thought that these antibodies might be a marker for predicting more severe disease. In addition, although the patients in the study were similar to RA in terms of clinical course and DMARD requirement, radiological findings were concordant with PsA in all patients, and skin lesions and nail involvement were found in all patients.<sup>21</sup> In another study, Abdel Fattah et al. showed appearance of bone erosions and peripheral feature disorders related to significant radiological changes in anti-CCP positive patients.<sup>23</sup> In our study, no significant difference was found between anti-CCP positive patients and anti-CCP negative patients in terms of clinical course and disease activities. In addition, no correlation was found between anti-CCP positivity and the presence of typical radiological findings (ankylosis, erosion, arthritis mutilans) in patients with peripheral arthritis. Also, in follow-up, no positive correlation was determined between anti-CCP positivity and whether remission was present in joint involvement.

### CONCLUSION

In this study, when the patients with PsA were evaluated in terms of anti-CCP positivity, it was detected higher anti-CCP concentrations than the control group. But as a clinical reflection of this, although different results were found in different studies, no significant difference was found in our study in anti-CCP positive PsA patients in terms of both disease activity and clinical course compared to anti-CCP negative PsA patients.

### Acknowledgements

None

### Conflict of Interest

None

### Funding

None

### Ethics approval

**The study was performed according to the Declaration of Helsinki. Kocaeli University ethical committee approved the study protocol (Date:27-12-2010, Approval Number:2010/4).**

### Author contributions

OOI, FC, AY and AC contributed to the conception and design of the study. Material preparation, data collection and analysis were performed by OOI. The first draft of the manuscript was written by OOI. All authors read and approved the final form.

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